

A Supportive Care Product for Parkinson's Disease Patients

NH004 – Treatment for Sialorrhea

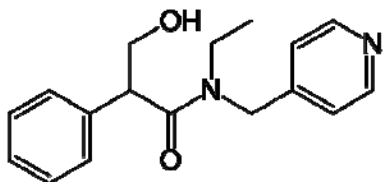
Summary

NH004 is a novel treatment to control the symptoms of sialorrhea (excessive drooling) in patients suffering from Parkinson's Disease and other motor disorders. NH004's active ingredient is the anticholinergic drug tropicamide, delivered in a thin film designed to adhere and slowly dissolve within the oral cavity to allow the drug to reach the underlying salivary gland, thereby reducing saliva secretions. The advantages of NH004 include local bioavailability with low systemic exposure, rapid onset of action and, importantly, convenience of use for patients. The active agent has a long history of safe topical ophthalmologic use in humans.

NH004 is currently in a double-blind phase II clinical testing in Parkinson's Disease patients, and is expected to be completed by the end of 2009. A planned interim analysis has indicated a difference in reducing sialorrhea between the NH004 treated and placebo groups. This clinical trial is being funded by the Michael J Fox Foundation.

Mechanism of Action

The active pharmaceutical ingredient in NH004 is tropicamide, a synthetic tertiary amine anticholinergic agent acting as a non-selective blockage to muscarinic receptors. Tropicamide is a fast-acting compound currently approved for use by the FDA as an ophthalmic solution for diagnostic procedures and surgeries. In sialorrhea, tropicamide acts by blocking the acetylcholine receptors of the salivary glands.



Active Ingredient: Tropicamide

N-ethyl-alpha-(hydroxymethyl)-N-(4-pyridinylmethyl)-benzeneacetamide

CAS number: 1508-75-4

Delivery System

NH004 contains tropicamide formulated in a novel and convenient drug delivery means known as thin films or “thin strips,” modeled on Listerine PocketPaks® breath strips, with two significant modifications: the film used in NH004 is formulated with a **muco-adhesive property** to adhere to the oral mucosa and allow the drug to be absorbed locally near the submandibular salivary gland. After placement in the mouth, the film **dissolves slowly** over a 60-90 minute period.



Listerine®

NH004

An attractive feature of NH004 films is the ability to readily modify the amount of the drug and excipients (such as flavors) or change the dissolution rate, and thereby differentiate a spectrum of marketable products.

Market Segments and Size

Sialorrhea is one of the major non-motor complaints in many patients suffering from various neurological impairments, including Parkinson’s disease, cerebral palsy, ALS, stroke and traumatic brain injury. Sialorrhea is often described by these patients as one of the most significant disabling social problems of their disease and not discussed due to the embarrassing nature of the condition. Depending on its severity, drooling can result in medical disability, impaired speech or serious eating difficulties.

Sialorrhea may affect up to a million patients with diverse neurological diseases. It affects a large proportion of Parkinson’s disease (PD) patients, ranging up to 78% in advanced stages, with many PD patients considering drooling as their worst non-motor symptom. PD prevalence in the US is estimated at 1.2 million. Sialorrhea also affects up to 37% of patients with cerebral palsy, the US prevalence of which is estimated at 500,000. Other large target populations include millions of survivors of stroke and severe traumatic brain injury.

Existing approaches to treating sialorrhea are not satisfactory. These include surgical procedures, prosthetic devices, botulinum toxin injections, systemic anticholinergic drugs, and speech and behavioral therapy. No single therapy satisfactorily resolves sialorrhea in all patients. There are also several ‘off label’ drug approaches to treat sialorrhea, including atropine, glycopyrrolate and ipratropium bromide spray. Each of these treatments has several shortcomings impeding their use and they have not gained any general acceptance.

NeuroHealing is aware of three approaches for the treatment of sialorrhea currently being tested: Solstice Neurosciences is sponsoring a trial of intra-glandular injections of botulinum toxin type B (Myobloc™), for the treatment of sialorrhea in adult PD patients; Sciele Pharma (acquired by Shionogi) has completed Phase III testing of pediatric doses of glycopyrrolate (oral liquid) for the treatment of profuse, severe drooling in patients with cerebral palsy in children up to 18 years of age; and Summit tested a combination product of two off patent drugs ($\alpha 2$ adrenoreceptor agonist

and anti-muscarinic agent) to treat sialorrhea, with a current focus now on developing a buccal formulation of these agents.

NeuroHealing estimates that an NDA could be filed for NH004 for Parkinson’s Disease patients by 2012. The company believes the potential annual US market size is approximately \$400 million for PD patients and that the initial marketing would be to neurologists and movement disorders specialists.

Intellectual Property

NeuroHealing owns multiple patent applications for the NH004 film composition and the use of intra-orally delivered tropicamide and/or anticholinergic agents. One published application, WO 2006/078998 “Methods and Compositions for Decreasing Saliva Production” claims compositions for the treatment of sialorrhea as well as to provide a dry oral field, such as during dental procedures, in otherwise healthy individuals. In addition, the company has proprietary know-how related to the manufacture and delivery of muco-adhesive slow-dissolving thin strips containing anticholinergic agents.

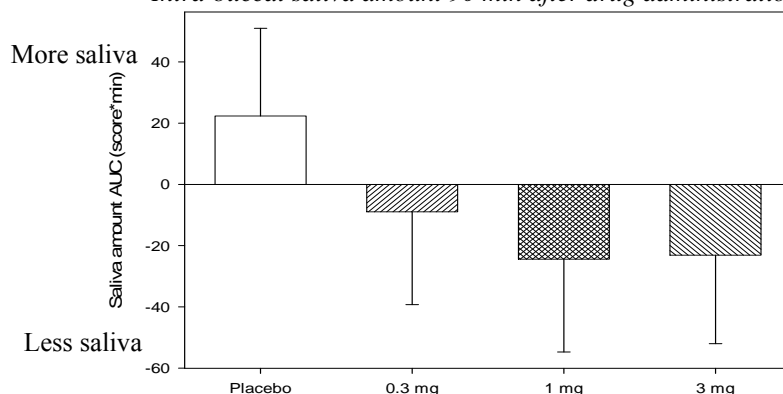
Development Status

NeuroHealing’s exploratory clinical tests have demonstrated encouraging results in reducing sialorrhea. In Parkinson’s patients complaining of sialorrhea, a clinically effective reduction of saliva was observed with no side effects or complications.

NeuroHealing is currently conducting a phase II, dose response, double-blind, placebo-controlled crossover study testing NH004 in up to 36 PD patients, with an expected completion in 2009 (www.clinicaltrials.gov/show/NCT00761137). A planned interim analysis in the first 12 patients has indicated that the maximal differences between NH004 and placebo were observed between 60-90 min post-dose, with a consistent dose-response trend. This trial is being funded by a clinical grant to NeuroHealing from the Michael J. Fox Foundation.

NH004-2 12-Patient Interim Results

Intra-buccal saliva amount 90 min after drug administration (VAS)



Upon a positive outcome of the on-going phase II trial, NeuroHealing plans to conduct a phase IIb study in the US in 2010, and initiate the phase III pivotal trials in early 2011.